of reversible causes may potentially reduce or prevent this infection.

554

ALTERNATING REGIMEN HYPER CVAD + IMATINIB IN PH (+) ALL PATIENT ON HIGH-FLUX DIALYSIS

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Lack of pharmacokinetic data on chemotherapy clearance in high flux hemodialysis hinders safe and effective dosing. We present a case of a 58 year old female diagnosed in September 2009 with Ph (+) ALL and a past medical history of focal segmental glomerular sclerosis on hemodialysis. The patient intially presented with worsening renal function, fevers and peripheral blasts. Upon diagnosis of Ph (+) ALL, the decision was made to treat with Hyper CVAD, a regimen of hyper fractionated cyclophosphamide, doxorubicin, vincristine and dexamethasone (odd cycle) alternating cycles with high dose methotrexate and high dose cytarabine (even cycle). High flux hemodialysis is relatively new, utilizing improved membranes that efficiently remove low molecular weight solutes and that are more effective at removing medium and high molecular weight solutes. Currently the dosing recommendations for chemotherapy are based on low flux hemodialysis. Weighing the potential for improved solute clearance and manufacturer dosing recommendations, no dose adjustments were made for the odd cycles of Hyper CVAD. Imatinib was started at 100 mg for cycle 1, titrated up to 200 mg by cycle 3 and increased to 400 mg at completion without side effects. Methotrexate is poorly removed by low flux hemodialysis and only one case report in a single patient provides pharmacokinetic information on removal by high flux hemodialysis. For even cycles of Hyper CVAD the methotrexate was initially dosed at 200 mg/m2, determined by estimating a dose cleared by 1 high flux hemodialysis session using the time averaged clearance reported in the case report by Murashima and colleagues. The methotrexate was adequately removed based on serum levels and patient tolerance. The dosage was increased to 500 mg/m2 for subsequent cycles. Further dose escalation was halted due to development of febrile neutropenia requiring hospitalization. Cytarabine was dosed at 100 mg/m2 continuous infusion for cycle 1 and increased to 200 mg/m2 base on manufacturer recommendations. The patient tolerated 8 cycles of Hyper CVAD with minimal side effects and 2 admissions for neutropenic fever. Complete remission was documented in December 2009. She remained in remission for 4 months after completion in April 2009. Recently reinduced with Hyper CVAD, peg asparaginase, and dasatinib with documented molecular remission.

555

DRUG-DRUG INTERACTION BETWEEN TACROLIMUS AND AZOLE ANTIFUNGAL AGENTS, ITRACONAZOLE AND VORICONAZOLE, IN ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION RECIPIENTS

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Background: The blood concentration of tacrolimus (TAC) is known to be increased by concomitant administration of voriconazole (VRCZ) and itraconazole (ITCZ), azole anti-fungal agents. We investigated changes in blood concentrations of TAC before and after concomitant administration of VRCZ or ITCZ to examine the optimal timing for monitoring blood concentrations of TAC.

Patients and Methods: We studied retrospectively patients who underwent hematopoietic stem cell transplantation between April 2004 and June 2010 and started VRCZ or ITCZ use during TAC administration. In a total of 34 patients receiving concomitant administration of VRCZ (tablets, n = 27; intravenous injection, n = 7) and 11 receiving ITCZ (capsules [Cap], n = 8; oral solution [OS], n = 3), the concentration/dose (C/D) ratio of TAC was observed from 10 days before through 35 days after the initiation of VRCZ or ITCZ.

Results: In all VRCZ group patients, C/D ratios of TAC increased after initiating VRCZ as compared with those before (median, 293%; range, 131%-923%; $P < 0.001$). Median time to reach the peak C/D ratio was 8 days (range, 3-30 days). When a loading dose was applied, the peak reached earlier (median, 6 days vs. 9.5 days; $P = 0.026$). Then C/D ratios decreased from peak (median, 50%; range, 23%-98%; $P < 0.001$). In 10 patients in the ITCZ group, the C/D ratio increased after initiating ITCZ as compared with those before (median, 267%; range, 141%-828%; $P < 0.001$). Median time to reach the peak C/D ratio was 19.5 days (range, 10-32 days). Patient who applied a loading dose was none. The rates of C/D ratio increase differed significantly between Cap and OS (median, 221% [range, 38%-475%] vs. 513% [range, 440%-828%]; $P = 0.025$) and times to reach the peak C/D ratio were similar (median, 20 days vs. 19 days).

Conclusions: In the VRCZ group, since blood concentrations of TAC transiently increased and then decreased, suggesting that careful monitoring is required even after dose reduction. It is also suggested that the optimal times for careful monitoring differ depending on whether or not the loading dose is applied. In the ITCZ group, the effects tended to appear after about 1 week. Significant increases in blood concentrations of TAC were observed in patients who received ITCZ by OS.

556

CORRELATION OF PATIENT CHARACTERISTICS INCLUDING AGE, OBESITY, GENDER AND RACE ON THE METABOLISM OF BUSULFAN

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Background: Busulfan, in myeloablative doses, is commonly used in conditioning regimens prior to hematopoietic stem cell transplantation (HSCT) and is associated with HSCT related toxicity including hepatic veno-occlusive disease (VOD). Busulfan is predominantly metabolized by conjugation with glutathione, both spontaneously and by glutathione S-transferase catalysis. Busulfan dosing is commonly adjusted using therapeutic drug monitoring (TDM) to limit toxicities. Whether patient characteristics such as race, age, obesity, gender and prior chemotherapy can influence the metabolism of busulfan remains unclear.

Methods: A retrospective chart review was conducted in 302 patients receiving intravenous busulfan between April 26th, 2001 and September 23rd, 2010. Data was obtained from an IRB approved busulfan TDM database and included gender, race, age, weight, height, BSA, BMI and elimination half-life obtained with the 1st dose of busulfan.

Results: Demographics included 172 males and 130 females, of which there were 222 Caucasians, 50 African Americans and 30 patients of other races. The mean age was 43 with 113 patients greater than 50 years old. Thirty patients weighed over 100 kg, 6 had a BMI < 18.5, 175 had a BMI of 18.5 – 29.9 and 122 had a BMI > / = 30. The mean half-life for all patients was 188 minutes (ranging 108 to 640 minutes). For the 12 patients with a BSA of 2.5 to 3.29, the mean half-life was 206 minutes (ranging 184 to 238 minutes). The half-lives for the small to large BMI groups were 186, 188 and 186 minutes. The half-life for females was 180 minutes vs. 194 minutes for males. The half-lives for Caucasians, African Americans and other races were 187, 194 and 182 minutes, respectively. Patients over 50 years old had a mean half-life of 189 minutes. For the entire group, wide variations in clearance were observed with 11% of patients having a half-life > 230 and 8% < 145 minutes. The maximum and minimum half-lives were 640 and 108 minutes.

Conclusion: Initial analysis of our data suggests that different dosing strategies based on population specific parameters may not be necessary. Pharmacists should continue to dose busulfan according to their institutional guidelines but due to the wide variations